10 reasons why it makes sense to rename DCIS to minimise overtreatment?

PRO: Mike Dixon OBE
Edinburgh Breast Unit
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PRO: Mike Dixon OBE
Edinburgh Breast Unit
What do we know about DCIS?
1. DCIS is a Disease of Breast Screening

It hardly existed as a clinical entity pre Screening
Incidence of DCIS and Localised Breast Cancers in USA

500% Increase in DCIS cases over past 25 years
Diagnosing More DCIS has NOT reduced the incidence of subsequent Invasive Breast Cancer

It has not reduced the incidence of late stage disease much either
Incidence of Breast Cancer

Age <40 years<br>
Age ≥40 years

- Incidence increasing in older not younger women
  - because of Breast Screening
- Over diagnosis is inescapable and magnitude large
Have we lost our way with Breast Screening?

If Women controlled medicine

The Manogram

"Who's been fooling around with these x-rays?"
2. We over diagnose and over treat because not all DCIS progresses to Invasive cancer

The % progression rate may be small
What % Of DCIS Lesions progress to Invasive Cancer?

- Knowing DCIS incidence and SEER rate of Invasive Breast Cancers
- Can estimate % DCIS cases that progress to Invasive Breast Cancer

3. We over treat DCIS because we call it cancer

A higher percentage of screen detected DCIS lesions are treated by mastectomy than Invasive Breast Cancers
Number of DCIS Cases in UK Treated by Mastectomy

20% of mastectomies are for DCIS which measures less than 20mm
The first rule of medicine is first do no harm
Mastectomy Rates over Time

UK Mastectomy rates in 2011/12
Invasive = 23%
Invasive <15mm = 15%
Non/micro-invasive = 27%

Changes in UK mastectomy rates with time
4. Further Support that many DCIS lesions are harmless and NOT Cancer comes from the declining death rate of DCIS.

Because most of it is not Cancer as we know it.
Death Rate from DCIS

Ernster et al Arch Int Med 2000:160; 953-8
SEER database 1525 women 1978-83, 5547 women 1984-89

<table>
<thead>
<tr>
<th>Interval</th>
<th>1978-83</th>
<th>1984-89</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>1.5%</td>
<td>0.7%</td>
</tr>
<tr>
<td>10 years</td>
<td>3.4%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

- 1.8% died from Breast Cancer in NSABP B17 @ 8 years
- 96% survival @15y in single centre with WLE + XRT
Despite the declining death rate the anxiety levels of women with DCIS are extremely high
What do women understand about DCIS?

Rakovitch et al Breast Cancer Res Treat 2003: 77; 285-93

- Same levels of anxiety and depression as T1/2 cancers
- Both groups estimated risk of dying to be 27%
5. This over diagnosis is supported by DCIS being a common finding in post mortem series

If it causes no problems in so many women:

Why do we need to diagnose and treat it?
Results from Autopsy Series

Welch et al Ann Intern Med 1997: 127; 1023-8

Seven Series of women without Breast Cancer

- Prevalence of Invasive Cancer 1.3% Range 0-18%
- Prevalence of DCIS 8.9% Range 0-14.7%
  - Range 7-39% in women 40-70 years of age
- Sections examined ranged from 7-275
- When >50 slides examined DCIS prevalence 14.5%
6. ADH and DCIS is a spectrum; it is not 2 separate conditions

One pathologists ADH is another pathologists DCIS
How do you differentiate ADH and DCIS?

- Need ≥2 Complete spaces or >2mm of disease
  - Problem cases

Single Duct <2mm so ADH

Single Duct >2mm so DCIS
No scientific basis for 2 spaces or 2mm
Sampling a Huge Issue
Single 1.5mm duct with classic cribriform nuclear grade 1 pattern; no necrosis

1. What is diagnosis?
   - 31.3% __ DCIS
   - 68.7% __ ADH

2. What is diagnosis if the duct were 0.5mm?
   - 22.6% __ DCIS
   - 77.4% __ ADH

3. What is diagnosis if the duct were 4mm?
   - 94.8% __ DCIS
   - 5.2% __ ADH
Partial Duct Involvement
A duct has partial involvement by cribriform pattern <1mm from a disease margin.
1. What is diagnosis?
   - 43.5% DCIS
   - 56.5% ADH

2. Would you advise Re excision?
   - 73% Yes
   - 27% No
Why should size or extent matter

It is the biology of the lesion that counts
We have already reclassified ALH and LCIS as LIN

DCIS and LCIS BOTH arise in the TDLU
Why do we think we should split ADH and DCIS into 2 groups yet combine ALH and LCIS?

We already have pleomorphic DCIS
We can have DIN and high grade DCIS
7. Genetic Changes in ADH and low grade DCIS are the same
Is ADH a Neoplasm?


• It is a new growth and not reversible

• Progresses to a distinct type of invasive carcinoma, albeit rarely

• Clonality identified in 37-40% by detection of LOH on at least 1 of 15 loci

• 70% flat epithelial atypia shows same LOH as DCIS
Loss of Heterozygosity

- O’Connell et al. 1998 Examined 399 lesions at 15 loci known to exhibit LOH in IBC
8. Rate of progression of Low and High Grade DCIS to Invasive Cancer is very different
Current Understanding

**INDOLENT**
- Atypia/Grade 1 CIS
  - Grade 1 Early stage

**SLOWLY PROGRESSIVE**
- Atypia/Grade 2 CIS
  - Grade 2 Early Stage
  - Late Stage
  - Death

**RAPIDLY PROGRESSIVE**
- High Grade CIS
  - Grade 3 Early Stage
  - Late Stage
  - Death
Risk Of In Breast Events and Invasive Cancer Events in Oncotype DCIS study

327 DCIS Lesions <2.5cm: 216 Low/Int Grade 111 High Grade Treated with WLE: 231 No Tam

ANY IBE

INVASIVE IBE

Solin LJ et al. JNCI 2013
9. Rate of Events in Women with low risk or low Grade DCIS similar to that of an at risk population
Postmenopausal women:
- Ages 40-70
- Increased risk of breast cancer:
  - Family history
  - Atypia / LCIS
  - Breast density
  - No HRT

IBIS 2 Trial schema

N=3864

Anastrozole 1 mg/day (N=1920)
5 years

Matching placebo (N=1944)
Breast Cancer Incidence in IBIS 2

All breast cancer: HR=0.47 (0.32-0.68), P<0.0001
ER+-invasive: HR=0.42 (0.25-0.71), P=0.001

<table>
<thead>
<tr>
<th>Follow-up time [years]</th>
<th>Placebo</th>
<th>Anastrozole</th>
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</thead>
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<tr>
<td>0</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>0.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>2</td>
<td>1.8%</td>
<td>5.6%</td>
</tr>
<tr>
<td>3</td>
<td>3.1%</td>
<td>7.8%</td>
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<tr>
<td>4</td>
<td>4.4%</td>
<td>10.0%</td>
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<tr>
<td>5</td>
<td>5.1%</td>
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<tr>
<td>6</td>
<td>5.5%</td>
<td>11.3%</td>
</tr>
<tr>
<td>7</td>
<td>5.6%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Number at risk
Placebo 1944 1927 1645 1445 1241 975 706 506
Anastrozole 1920 1909 1654 1463 1264 978 720 516
Probability of Cancer After Atypia Diagnosis With and Without Chemoprevention


n=466 w chemoprevention
n=1472 without chemoprevention
## Magnitude of Risks for Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>10 year ipsilateral</th>
<th>5 year ipsilateral</th>
<th>Lifetime (either breast)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LIN</strong></td>
<td>5-10%</td>
<td>3-5%</td>
<td>20-40%</td>
</tr>
<tr>
<td><strong>Atypia</strong></td>
<td>5-10%</td>
<td>3-5%</td>
<td>20-40%</td>
</tr>
<tr>
<td><strong>Low Risk DCIS</strong></td>
<td>4-7%</td>
<td>2.5%**</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>Int Risk DCIS</strong></td>
<td>7-12%</td>
<td>4-5%**</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>High Risk DCIS</strong></td>
<td>15-20%</td>
<td>7**-15%</td>
<td>15-30%</td>
</tr>
<tr>
<td><strong>BRCA 1/2</strong></td>
<td></td>
<td>5-7%</td>
<td>50-85%</td>
</tr>
</tbody>
</table>
10. Lessons from other organs

We need to follow their lead
1998 Classification revised from 1973 version

- Grade 1 carcinoma → PUNLMP (papillary urothelial neoplasia of low malignant potential)

_the word carcinoma has been removed_

- why call it carcinoma if risk of disease recurrence and progression are both very low?
Need to Reclassify Low and Intermediate grade Grade DCIS together with ADH as single entity

They are Risk lesions NOT cancer

I favour DIN rather than IDLE
High Grade DCIS is a different Entity

- Not all high grade DCIS lesions are the same
- Need to better define the most high risk
  - Are some really invasive
  - Or do we just miss the invasion

- Neoductgenesis dense areas of DCIS with calcs
  - Subgroup with poor outcome
Why change the name?

- Cancer emotive word
- Massively increases anxiety
- Causes doctors to discuss all options
- Patients having bilateral mastectomy in UK and USA for low grade DCIS but not for LIN unless + FH
- More consistent diagnosis by pathologists
- It’s time to change